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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/309,689	05/11/99	ORENTREICH N	4555-45

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EXAMINER	
MOHAMED, A	
ART UNIT	**PAPER NUMBER**
1653	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/309,689	Applicant(s) ORENTREICH ET AL
	Examiner MOHAMED	Group Art Unit 1653

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -3- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 1/8/01.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-22 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4 (1 page) ☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other _____

Office Action Summary

DETAILED ACTION

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, IDS AND STATUS OF THE CLAIMS

1. The amendment, remarks, Information Disclosure Statement (IDS) and Form PTO 1449 filed 1/8/01 are acknowledged, entered and considered. In view of Applicant's request claims 9 and 11 have been amended. Thus, claims 1-22 are now pending in the application. The objection to Trademarks and the rejection under 35 U.S.C. 112, second paragraph are withdrawn in view of Applicant's amendment and remarks filed 1/8/01. However, the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) over the prior art of record are maintained.

CLAIMS REJECTION-35 U.S.C. § 102(b)

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-6, 8 and 22 remain rejected under 35 U.S.C. 102(b) as being anticipated by Coleman III, et al. ([eds.] Skin resurfacing, pp. 217-234, 1998).

The instantly claimed invention as claimed in claims 1, 5-6, 8 and 22 is directed to an injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins (claim 1), wherein the cross-linked blood plasma proteins are purified and sterilized or dialyzed and autoclaved (claims 5-6), wherein the material further comprises one or more additional components selected from group consisting of anesthetic compound, vitamins, growth factors, and enzyme inhibitors (claim 8), and injecting the material into an intradermal compartment of the skin of the mammal (claim 22).

Similarly, the reference of Coleman III, et al. is directed like the instantly claimed invention to an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins which are purified and sterilized. The reference shows the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient (See e.g., page 222 under the heading FIBREL). Thus, the reference clearly anticipates the use of an injectable material comprising cross-linked, blood plasma proteins for soft tissue augmentation as drafted in claims 1, 5-6, 8 and 22.

3. Claims 1, 5-6, 8 and 22 remain rejected under 35 U.S.C. 102(b) as being anticipated by Pollack (J. Dermatol. Surg. Oncol., Vol. 16, No. 10, pp. 957-961, October 1990).

The instantly claimed invention as claimed in claims 1, 5-6, 8 and 22 is directed to an injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins (claim 1), wherein the cross-linked blood plasma proteins are purified and sterilized or dialyzed and autoclaved (claims 5-6), wherein the material further comprises one or more additional components selected from group consisting of anesthetic compound, vitamins, growth factors, and enzyme inhibitors (claim 8) and injecting the material into an intradermal compartment of the skin of the mammal (claim 22).

Similarly, the reference of Pollack is directed like the instantly claimed invention to an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins which are purified and sterilized. The reference shows the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient (See e.g., page 960 under the heading FIBREL). Thus, the reference clearly anticipates the use of an injectable material comprising cross-linked, blood plasma proteins for soft tissue augmentation as drafted in claims 1, 5-6, 8 and 22.

CLAIM REJECTIONS-35 U.S.C. § 103(a)

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Coleman III, et al. ([eds.] Skin resurfacing, pp. 217-234, 1998) or Pollack (J. Dermatol. Surg. Oncol., Vol. 16, No. 10, pp. 957-961, October 1990) in view of Grabarek et al. (Analytical Biochemistry, Vol. 185, pp. 131-135, 1990) or Wong (Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207, 1991) or Wang et al. (Journal of the Parenteral Drug Association, Vol. 34, No. 6, pp. 452-462, November-December 1980).

The instantly claimed invention as claimed in claims 1-22 is directed to an injectable material comprising blood plasma proteins which are cross-linked with a zero-length-cross-linking agent and that the cross-linked proteins are purified and/or sterilized and the blood protein can be obtained from an autologous blood sample, and to a method of preparing an injectable material thereof as well as injecting the material into an intradermal compartment of the skin of the mammal.

The primary references of Coleman III, et al. or Pollack as discussed above in the rejections under 35 U.S.C. 102(b) discloses like the instantly claimed invention an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins which are purified and sterilized. The references show the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient.

Coleman III, et al. or Pollack differ from claims 1-22 in not teaching the use of a cross-linked blood plasma proteins which comprise zero-length cross-linked, blood plasma proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond and the ratio of cross-linked, plasma proteins is from 1% to about 10% by weight of injectable material to the physiological acceptable fluid of from 99% to about 90% by weight of the injectable material. However, use of cross-linking agents are known in the art, particularly, such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) for the purpose of crosslinking protein-protein complexes as taught by Garbarek et al. The reference teaches on page 131 that the zero-length crosslinking procedure with the use of active esters such as EDC for inducing isopeptide bonds between amino acid side chains in proteins in aqueous solution. The reference also states that the crosslinking agent should be used at a 5-to 10-fold dilution than the complexed protein and as such overlaps with the amounts disclosed in claim 7. Further, on page 134, bridging page 135, the reference clearly shows that zero-length crosslinking with carbodiimides intramolecular crosslinking can occur if there are

$NH+_3$ - COO- interaction with the protein. Such interactions are known to be involved in stabilization of the 3D structure of proteins as, for example, in the "I to I +4" type interactions between Lys and Glu (or Asp) side chains in α-helical segments. Thus, clearly showing that the amide bond cross-link comprises a lysine-glutamate amide bond or a lysine-aspartate amide bond, and as such meets the limitation of claim 4. Furthermore, the reference of Wong discloses the various zero-length cross-linking reagents under A to E for the purpose of inducing the direct joining of, and create sable bonds between, two intrinsic chemical moieties of one or more polypeptide chains, without the introduction of any extrinsic matter (See e.g. pages 195-202). Thus, the reference meets the limitations of claim 17. Moreover, the reference of Wang et al. reviews the various excipient (additives) and pH's for parenteral products in which the reference focuses on products with extreme pH's, and shows the tabulation of pH range, acid or base used for adjustment, and product identity. The reference also discloses numerous physiological acceptable fluid as additives for parenteral formulations which includes anesthetic compounds such as procaine among others (See e.g., the entire document and particularly pages 452 and 460).

Therefore, given the teachings of the primary references, one of ordinary skill in the art would have been motivated to adapt the above scheme of using of a cross-linked blood plasma proteins which comprise zero-length cross-linked, blood plasm proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond. Furthermore, such features are known or suggested in the art, as

seen in the secondary references, and including such features into the injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins of the primary references of Coleman III, et al. or Pollack would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof. Thus, in view of the above, and in view of the combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked with a zero-length-cross-linking agent such as EDC as discussed in the secondary references for the intended purpose of obtaining or producing a safe , non-antigenic, non-irritating, longer-lasting and aesthetically-pleasing injectable materials for soft tissue augmentation which are relatively easy to obtain and/or manufacture.

Accordingly, claims 1-22 are prima facie obvious over the prior art, because it would be within the ordinary skill of the art to easily adapt the already known system of zero-length crosslinking procedure described in the prior art of the secondary references which is applicable to all kinds of proteins including blood plasma proteins for the intended purpose of cross-linking blood plasma proteins to form materials which are injectable and could be used in a method of augmenting a soft tissue defect in a skin area of a mammal by injecting the material into an intradermal compartment of the skin of the mammal is an obvious modification of the prior art combined teachings at the time the invention was made, absent of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 102(b)

5. The rejection of claims 1, 5-6, 8 and 22 under 35 U.S.C. 102(b) as being anticipated by Coleman III, et al. ([eds.] Skin resurfacing, pp. 217-234, 1998).

Applicant's arguments filed 1/8/01 have been fully considered but they are not persuasive. Applicant's arguments that the plasma carrier fluid disclosed in the reference may incidently contain blood plasma proteins is irrelevant, as such proteins are not cross-linked and therefore remain soluble. In contrast, the injectable material of the present invention contains cross-linked, blood plasma proteins which are insoluble and non-biodegradable, and can therefore act as a filler to argument the treated tissue. Accordingly, because Coleman does not teach each and every element of the claimed invention, the reference can not anticipate the claims is noted. However, contrary to Applicant's arguments the instantly claimed invention as claimed in claims 1, 5-6, 8 and 22 is directed to an injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins (claim 1), wherein the cross-linked blood plasma proteins are purified and sterilized or dialyzed and autoclaved (claims 5-6), wherein the material further comprises one or more additional components selected from group consisting of anesthetic compound, vitamins, growth factors, and enzyme inhibitors (claim 8), and injecting the material into an intradermal compartment of the skin of the mammal (claim 22).

As discussed above the prior art of Coleman III, et al. clearly reads on composition claims 1, 5-6, 8 and method claim 22 as drafted because the reference discloses a composition

comprising cross-linked blood plasma proteins which are purified, sterilized, dialyzed, autoclaved and having additional components such as anesthetic compound useful for soft tissue augmentation. Thus, the reference clearly anticipates the use of an injectable material comprising cross-linked, blood plasma proteins for soft tissue augmentation as drafted in claims 1, 5-6, 8 and 22 in the express absence of evidence to the contrary or specific structural limitation.

6. The rejection of claims 1, 5-6, 8 and 22 under 35 U.S.C. 102(b) as being anticipated by Pollack (J. Dermatol. Surg. Oncol., Vol. 16, No. 10, pp. 957-961, October 1990).

Applicant's arguments that the plasma carrier fluid disclosed in the reference may incidently contain blood plasma proteins is irrelevant, as such proteins are not cross-linked and therefore remain soluble. In contrast, the injectable material of the present invention contains cross-linked, blood plasma proteins which are insoluble and non-biodegradable, and can therefore act as a filler to argument the treated tissue. Accordingly, because Pollack does not teach each and every element of the claimed invention, the reference can not anticipate the claims is noted. However, contrary to Applicant's arguments the instantly claimed invention as claimed in claims 1, 5-6, 8 and 22 is directed to an injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins (claim 1), wherein the cross-linked blood plasma proteins are purified and sterilized or dialyzed and autoclaved (claims 5-6), wherein the material further comprises one or more additional components selected from group consisting of anesthetic compound, vitamins, growth factors, and enzyme inhibitors (claim 8), and injecting the material into an intradermal compartment of the skin of the mammal (claim 22).

As discussed above the prior art of Pollack clearly reads on composition claims 1, 5-6, 8 and method claim 22 as drafted because the reference discloses a composition comprising cross-linked blood plasma proteins which are purified, sterilized, dialyzed, autoclaved and having additional components such as anesthetic compound useful for soft tissue augmentation. Thus, the reference clearly anticipates the use of an injectable material comprising cross-linked, blood plasma proteins for soft tissue augmentation as drafted in claims 1, 5-6, 8 and 22 in the express absence of evidence to the contrary or specific structural limitation.

CLAIMS REJECTION-35 U.S.C. § 103(a)

7. The rejection of claims 1-22 under 35 U.S.C. 103(a) as being unpatentable over Coleman III, et al. ([eds.] Skin resurfacing, pp. 217-234, 1998) or Pollack (J. Dermatol. Surg. Oncol., Vol. 16, No. 10, pp. 957-961, October 1990) in view of Grabarek et al. (Analytical Biochemistry, Vol. 185, pp. 131-135, 1990) or Wong (Chemistry of Protein Conjugation and Cross-linking, pp. 39-40 and 195-207, 1991) or Wang et al. (Journal of the Parenteral Drug Association, Vol. 34, No. 6, pp. 452-462, November-December 1980).

Applicant's arguments that none of the cited references either alone or in combination teaches, discusses, or suggests use of the disclosed processes or reagents to produce an injectable material for tissue augmentation comprising cross-linked blood plasma proteins is not persuasive. Contrary to Applicant's arguments, the primary references of Coleman III, et al. or Pollack as discussed above in the rejections under 35 U.S.C. 102(b) discloses like the instantly claimed

invention an injectable material for soft tissue augmentation of wrinkles comprising cross-linked, blood plasma proteins which are purified and sterilized. The references show the administration of the injectable material in combination with an anesthetic compound such as lidocaine into an intradermal compartment of the skin of a patient. Thus, the primary references clearly teach the use of injectable material for tissue augmentation comprising cross-linked blood plasma proteins.

Applicant assertion that even if the Examiner's suggested combination did teach or suggest each and every element of the claimed invention, which they do not, such combination do not render the claimed invention obvious, for there was no motivation or suggestion in the art to combine references as suggested by the Examiner to arrive at the present invention is noted. However, Applicant's assertion is unpersuasive because given the teachings of the primary references, one of ordinary skill in the art would have been motivated to use cross-linking agents which are known in the art and taught by the secondary references as discussed above and adapt the above scheme of using of a cross-linked blood plasma proteins which comprise zero-length cross-linked, blood plasm proteins, wherein the zero-length cross-linked blood plasma proteins contain an amide bond cross-link such as lysine-glutamate bond or lysine-aspartate bond. Furthermore, such features are known or suggested in the art, as seen in the secondary references, and including such features into the injectable material for soft tissue augmentation in mammals comprising cross-linked, blood plasma proteins of the primary references of Coleman III, et al. or Pollack would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof. Thus, in view of the above, and in view of the

combined teachings of the prior art; one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known injectable material for soft tissue augmentation comprising cross-linked, blood plasma proteins which are cross-linked with a zero-length-cross-linking agent such as EDC as discussed in the secondary references for the intended purpose of obtaining or producing a safe , non-antigenic, non-irritating, longer-lasting and aesthetically-pleasing injectable materials for soft tissue augmentation which are relatively easy to obtain and/or manufacture.

Thus, the combined teachings of the prior art clearly teach the use of an injectable material comprising blood plasma proteins which are cross-linked with a zero-length-cross-linking agent and that the cross-linked proteins are purified and/or sterilized and the blood protein can be obtained from an autologous blood sample, and to a method of preparing an injectable material thereof as well as injecting the material into an intradermal compartment of the skin of the mammal. Therefore, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the prior art teachings would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

ACTION IS FINAL

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION WITH FUTURE CORRESPONDENCE

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher S. F. Low
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Mohamed/AAM

March 23, 2001